REMARKS

The Office Action of December 18, 2002 has been received and reviewed. Claims 1-11, 18-22, 27 and 35-46 are pending in the application. All claims stand rejected. Claims 1, 3, 18, 20, 22 and 27 have been amended, claims 2, 4-17, 19, 21, 23-26 and 28-46 have been canceled, and new claims 47-50 have been added as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Drawings

It was noted that the application contains color photographs. Submitted herewith is a petition under 37 C.F.R. § 1.84(a)(2) requesting approval of the color drawings. Also submitted herewith is the fee of $130.00 set forth in 37 C.F.R. § 1.17(h), three sets of color drawings and a black and white photocopy of the color drawings that accurately depicts, to the extent possible, the subject matter of the color drawings. The brief description of the drawings in the specification has been amended to include the appropriate language.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-11, 18-22, 27 and 35-46 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 2, 4-11, 19, 21 and 35-46 have been canceled rendering the rejections thereof moot. Applicants have amended the remaining claims. At least partially in view of the amendments to the claims, applicants respectfully traverse the rejections.

Specifically, the claims were thought to be vague and indefinite for including the recitation "fibroblast-like or macrophage-like cells." It was further thought to be unclear what type of cells the claims embrace. Although applicants do not agree that the claims are indefinite, for the sake of expedited prosecution, claim 1 has been amended to recite in part "fibroblast-like or macrophage-like cells associated with a synovial cavity" to clarify that the recombinant adenovirus has a tropism for fibroblast-like and macrophage-like cells associated with the synovial cavity which is supported by the as-filed specification. (*See*, Specification, page 23).

It was also thought that the phrase "partially reduced tropism" was unclear. Although applicants do not agree that the phrase is unclear, it has been removed from the claims thus obviating the rejections.

The recitation of deprived "at least in part" of claim 3 was also thought to be unclear. Claim 3 has been amended to recite in part "wherein said subgroup C adenovirus is adenovirus 5." Thus, claim 3 should be definite.

Claim 27 was deemed indefinite since it was thought that steps were missing from the method. It was asserted to be unclear how the vehicle is introduced to the particular cells. Although applicants do not agree that claim 27 is indefinite, for the sake of expedited prosecution, claim 27 has been amended to recite in part "introducing a recombinant adenovirus having a tissue tropism for fibroblast-like or macrophage-like cells associated with a synovial cavity into the synovial cavity; wherein the recombinant adenovirus's capsid includes at least one protein of an adenovirus of subgroup C origin and at least a knob domain of a fiber protein of adenovirus 16 associated therewith; and allowing the recombinant adenovirus to infect the fibroblast-like or macrophage-like cells associated with the synovial cavity" to render claim 27 definite.

Reconsideration and withdrawal of the indefiniteness rejections of claims 1, 3, 18, 20, 22 and 27 are requested.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1-11, 18-22, 27 and 35-46 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Claims 2, 4-11, 19, 21 and 35-46 have been canceled rendering the rejections

thereof moot. The remaining claims have been amended. At least partially in view of the amendments to the claims, applicants respectfully traverse the rejections.

Specifically, the phrase "fibroblast-like or macrophage-like cells" was thought to be insufficiently defined. Claim 1 has been amended to recite in part "fibroblast-like or macrophage-like cells associated with a synovial cavity" to clarify that the recombinant adenovirus has a tropism for the cells associated with the synovial cavity. Since the claims and the specification are used to ascertain whether the disclosure satisfies the written description requirement (*See generally*, M.P.E.P. § 2136) and the specification indicates that the recombinant adenoviruses are used to introduce genetic material into fibroblast-like or macrophage-like cells, such as synoviocytes (*See*, Specification, p. 9), one of skill in the art could only conclude that the inventors had possession of the amended claims.

The Office also asserted that the specification failed to provide an adequate written description for claims reciting a reduced tissue tropism for liver cells. The specification recites in part "the invention provides an adenovirus capsid with a reduced or having at least in part been deprived of a tissue tropism for liver cells." (*See*, *Id.* at p. 23). Accordingly, one of skill in the art would conclude that the inventors had possession of a recombinant adenovirus with a reduced tissue tropism for liver cells.

It was further asserted that the specification failed to teach what part of a virus capsid from two different viruses would provide the desired tropisms. Claim 1 has been amended such that the recombinant adenovirus includes at least one protein from an adenovirus of subgroup C and at least the knob domain of the fiber protein of adenovirus 16 associated with a capsid of the recombinant adenovirus. The amendment adopts the statement in the Office Action that "the described chimeric Ad5.Fib16 adenoviral vector meets the written description provision of 35 U.S.C. § 112, first paragraph" (Office Action, page 9) since Ad5 adenovirus is a subgroup C adenovirus.

In view of the amendments and remarks presented herein, reconsideration and withdrawal of the written description rejections of claims 1, 3, 18, 20, 22 and 27 are requested.

Enablement

Claims 1-11, 18-22, 27 and 35-46 further stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Claims 2, 4-11, 19, 21 and 35-46 have been canceled rendering the rejections thereof moot. At least partially in view of the amendments to the remaining claims, applicants respectfully traverse the rejections.

Specifically it was asserted by the Office that "the specification fails to teach whether Ad5.fib16 would target all fibroblast-like and macrophage-like cells other than synovial cells" and that "the specification is silent regarding the tissue tropism of other vectors, and whether incorporating an Ad5.Ad16 fiber protein would alter tissue tropism for all known vectors." (Office Action, pages 11-12).

As amended, claim 1 is directed to a recombinant adenovirus having a tissue tropism for fibroblast-like or macrophage-like cells associated with a synovial cavity, wherein the recombinant adenovirus's capsid includes at least one protein of an adenovirus of subgroup C origin and at least a knob domain of a fiber protein of adenovirus 16 associated therewith. The specification discloses that a recombinant adenovirus having a protein from a subgroup C adenovirus and at least the knob domain of the fiber protein of adenovirus 16 associated with the capsid was constructed. (*See, e.g.*, Specification, page 31, Examples 2 and 3 disclose Ad.Luc-fib16). The specification further indicates that the recombinant adenovirus Ad5.fib16.luc does, in fact, infect synoviocytes more efficiently than Ad5.luc. (*See, Id.*, page 68, Table XIII; *see also, Id.* at page 55, Examples 11, 12 and 13; *see also, Id.*, at Table XVI, page 69 indicating that Ad5.Fib16 infects synoviocytes more efficiently than other chimeric adenoviruses). Thus, claim 1 is enabled.

Regarding a reduced tissue tropism for liver cells, the specification indicates that the recombinant adenovirus Ad5.Luc-fib16 was injected into rats and as indicated in Table II, a smaller amount of luciferase activity was detected in the liver for Ad5.Luc-fib16 than with Ad5.Clip.Luc. (*See, Id.* at Table II, page 59). Thus, the reduced tissue tropism for liver cells is enabled.

Claims 1, 3-11, 18-22, 27, 36-42, 45 and 46 further stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement for delivering any vector having a chimeric viral fiber protein, via any route of administration, to any fibroblast-like or macrophage-like cells. Claims 4-11, 19, 21, 36-42, 45 and 46 have been canceled rendering the rejections thereof moot. As previously stated, applicants have amended the claims, and respectfully request that the rejections be withdrawn, at least partially in view of the amendments set forth herein.

More particularly, the Office Action indicated that the specification "while being enabling for preferentially delivering an adenoviral vector comprising a chimeric Ad5 and Ad16 fiber knob protein to synovial cells in vitro or in vivo ... does not reasonably provide enablement for delivering any vector, with any chimeric viral fiber protein, via any routes of administration, to any fibroblast-like or macrophage-like cells." (Office Action, page 12). Although applicants do not agree the claims are not enabled, to expedite prosecution of the application, claim 1 has been amended to read on a recombinant adenovirus including at least one protein from a subgroup C adenovirus and a knob domain of the fiber protein of adenovirus 16 associated with a capsid of the recombinant adenovirus, wherein the recombinant adenovirus has a tissue tropism for fibroblast-like or macrophage-like cells associated with a synovial cavity. Thus, as amended, claim 1 is enabled.

With regard to claim 27, the Office Action stated "the specification fails to teach the genus of vectors having said tissue tropism, whether any type of vector carrying an adenoviral vector fiber 16 would achieve the desired effect, whether the effect extends to any type of fibroblast-like or macrophage-like cells, whether any route of administration, such as intramuscular, intradermal, intravenous, and oral administration would also achieve the preferential transfection effect." (*Id.* at page 14). Regarding the genus of vectors and the tissue tropism, claim 27 has been amended to include a recombinant adenovirus that includes at least one protein from a subgroup C adenovirus and a knob domain of the fiber protein of adenovirus 16, thus, is enabled.

With regard to the route of administration, although applicants do not agree that claim 27 is not fully enabled, to expedite prosecution, claim 27 has been amended to recite in part "introducing a recombinant adenovirus having a tissue tropism for fibroblast-like or macrophage-

like cells associated with a synovial cavity into the synovial cavity" and "allowing said recombinant adenovirus to infect said fibroblast-like or macrophage-like cells associated with the synovial cavity." "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." (M.P.E.P. § 2164.01(b), *citing In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)). Since the specification discloses at least one method of using the recombinant adenovirus, *i.e.*, introducing recombinant adenovirus into the joints of monkeys where lacZ activity was observed, claim 27 should be enabled. (*See*, Specification, page 40 under heading "Possibility and specificity of gene transfer to inflamed synovial tissue *in-vivo*").

With further regard to claim 27, the Office Action stated "the specification fails to provide any therapeutic effect as a result of recombinant adv transfection even though the experiments were performed in an experimental arthritis model." (*Id.* at page 17). As amended, claim 27 is directed to a method of delivering a nucleic acid of interest to fibroblast-like or macrophage-like cells associated with a synovial cavity comprising introducing a recombinant adenovirus into the synovial cavity and allowing the recombinant adenovirus to infect the fibroblast-like or macrophage-like cells associated with the synovial cavity. As disclosed in the specification, treatment with the recombinant adenovirus, *e.g.*, a recA vector expressing the TK gene, is a feasible method of non-surgical synovectomy in arthritic joints since treatment with the recombinant adenovirus cause cells to undergo apoptosis. (*See*, Specification, pages 54-55).

As stated in the Office Action, the composition of the present invention, *i.e.*, the recombinant adenovirus of claim 1, is for "therapeutic use, to prevent, alleviate, treat, or cure a disease within the animal to which the substance is administered." (Office Action, page 14). Thus, all that is required is that the specification discloses a recombinant adenovirus that prevents, alleviates, treats, or cures a disease. Since a therapeutic use has been shown, *i.e.*, inducing apoptosis to effectively perform non-surgical synovectomy in arthritic joints (*See*, Specification, page 55), the claim should be enabled.

Reconsideration and withdrawal of the enablement rejections of claims 1, 3, 18, 20 and 27 are, thus, requested.

Rejections under 35 U.S.C. § 102

Maxwell et al.

Claims 1-4, 18, 27, 35, 36 and 43 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Maxwell et al. (U.S. Pat. 5,585,254). Claims 2, 4, 35, 36 and 43 have been canceled rendering the rejections thereof moot. Applicants respectfully traverse the rejections as hereinafter set forth.

It was noted in the Office Action that claims 9, 22, 40, 45 and 46 appeared to be free of art. (*See*, Office Action, page 25). Although applicants do not agree that the claims are anticipated, for the sake of expedited prosecution, claim 1 has been amended to recite in part "said recombinant adenovirus comprising ... at least a knob domain of a fiber protein of adenovirus 16 associated with the recombinant adenovirus's capsid." Thus, amended claim 1 is not anticipated since it includes elements of claims deemed free of the art.

Dependent claims 3, 18, 20, 22, 27 and 49 are novel, at the very least, as depending from novel independent claim 1.

Stevenson et al.

Claims 1-8, 10, 11, 18-21, 27, 35-38, 41, 43 and 44 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Stevenson et al. (J Virol 1997; 6:4782-90). Claims 2, 4-8, 10, 11, 19, 21, 35-38, 41, 43 and 44 have been canceled rendering the rejections thereof moot. Applicants respectfully traverse the rejection as hereinafter set forth.

As previously discussed herein, claim 1 has been amended to include the subject matter of claims deemed free from the art. Thus, claim 1 should not be anticipated.

Dependent claims 3, 18, 20 and 27 are novel, at the very least, as depending from novel independent claim 1.

Wickham et al.

Claims 1-6, 18, 35, 36 and 43 stand rejected under 35 U.S.C. § 102(e) as assertedly being anticipated by Wickham et al. (U.S. Pat. 6,329,190) as evidenced by Lazarovits et al. (J Immunol

1994; 151: 6482-9). Claims 2, 4-6, 35, 36 and 43 have been canceled rendering the rejections thereof moot. Applicants respectfully traverse the rejections as hereinafter set forth.

For the sake of expedited prosecution, claim 1 has been amended to include the subject matter of claim 9. Accordingly, claim 1 should not be anticipated since claim 9 was deemed free of the art.

Dependent claims 3 and 18 are novel, at the very least, as depending from novel independent claim 1.

Rejections under 35 U.S.C. § 103

Claims 1 and 27 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Wickham et al. Claims 1-4, 18, 27, 35, 36 and 43 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Goldsmith et al. (U.S. Pat. 5,861,290). Claims 2, 4, 35, 36 and 43 have been canceled rendering the rejections thereof moot. Applicants respectfully traverse the rejections as hereinafter set forth.

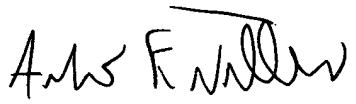
As amended, claim 1 should be free of the art since it was amended to include the subject matter of claim 9. Dependent claims 3, 18 and 27 are nonobvious, at the very least, as depending from nonobvious independent claim 1. (*See, In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)).

Reconsideration and withdrawal of the obviousness rejections of claims 1, 3, 18 and 27 are requested.

CONCLUSION

In view of the amendments and remarks presented herein, applicants respectfully submit that the claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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